

**REMARKS/ARGUMENTS**

Claims 44-50 are pending in this application. Claim 44 has been amended herein. Claims 1-43 and 51-72 have been canceled either previously or in this Amendment. Claims 44-50 stand rejected. The issues raised in the final Office Action of August 24, 2010 ("Current Action") are as follows:

- \*      Claims 44-50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite;
- \*      Claims 44-50 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification, written description;
- \*      Claims 44-50 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification, enablement;
- \*      Claims 44-46 are rejected under 35 U.S.C. § 102 (e) as being anticipated; and
- \*      Claims 44-47, 49, and 50 are rejected under 35 U.S.C. § 102 (b) as being anticipated.

In response, Applicant respectfully traverses the outstanding claim rejections and requests reconsideration and withdrawal in light of the remarks presented herein.

***REJECTIONS UNDER 35 § U.S.C. § 112***

*Claims 44-50 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite.*

The Current Action alleges that the claims are vague and indefinite in the recitation of "TNF $\alpha$ " stating that it appears unclear if Applicants are attempting to define other cytokines such as IL-4 as TNF $\alpha$ . For the sake of compact prosecution, the claim has been amended to make clear that TNF $\alpha$  is limited to human TNF $\alpha$  molecules and their equivalents but does not include any non-TNF $\alpha$  molecules. Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 112 second paragraph.

***Claims 44-50 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification, written description.***

The Current Action alleges that there is insufficient written description to show that Applicants are in possession of the TNF $\alpha$  of the claims. In particular, the Current Action alleges that no species of TNF $\alpha$  has been described because the source of the TNF $\alpha$  employed has not been described and no common structure or function is defined.

Applicants respectfully request that the Examiner withdraw the rejection of Claims 44-50 under 35 U.S.C. § 112 first paragraph because possession is shown by actual reduction to practice; furthermore, the present application discloses a source for TNF $\alpha$  employed. The MPEP unambiguously states that possession may be shown by describing actual reduction to practice of the claimed invention. *See* MPEP 2163 II, A, (3)(a).

Applicants submit that the present application, including Figures 1-19 demonstrate reduction to practice of the invention. Furthermore, the present application discloses the source of TNF $\alpha$  as being R&D (which is commonly recognized as abbreviation for R&D Systems, Inc, 614 McKinley Place NE, Minneapolis, MN 55413). *See* present application, p. 21. Therefore, Applicants have, without doubt, possession of the invention and of human TNF $\alpha$ .

For the sake of compact prosecution, the claim has been amended to recite human tumor necrosis factor alpha and its equivalent. Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 112 first paragraph.

***Claims 44-50 are rejected under 35 U.S.C. § 112, first paragraph, enablement***

The Current Action alleges that the present application is not enabled because the claims encompass a method (*i.e.*, generating DCs from monocytes employing GM-CSF and TNF $\alpha$ ) that has been unsuccessfully tried by Pickl et al. (hereinafter Pickl).

Applicants respectfully request that the Examiner withdraw the rejection of Claims 44-50 under 35 U.S.C. § 112 first paragraph, enablement, because the present

application meets the requirement for enablement; in addition, the rejection is improperly based on Official Notice.

The MPEP states that the enablement requirement refers to the requirement that the specification describes how to make and how to use the invention. MPEP2164. No matter how unsuccessfully Pickl tried to invent a subject matter, it does not change the fact that Applicants have invented and disclosed how to make and how to use the invention. The standard for enablement has no regard for a third party's failure; instead, enablement depends on whether the experimentation needed to practice the invention is undue or unreasonable. See MPEP2164.01. Accordingly, patent law does not allow Pickl's failure to generate additional burden for Applicants.

The Current Action takes official notice that (1) it is highly unlikely that Applicants succeeded where Pickl failed; and, (2) that it is well established that activation of T cells in an MLR context is much easier to perform than the activation of T cells in an antigen-specific context. The MPEP states that official notice unsupported by documentary evidence should only be taken where the facts asserted to be well-known, or to be common knowledge in the art, are capable of instant and unquestionable demonstration as being well-known. MPEP 2144.03 (citing *In re Ahlert*, 424 F.2d 1088, 1091, 165 USPQ 418, 420 (CCPA 1970) (holding that such notice must be "capable of such instant and unquestionable demonstration as to defy dispute")). The MPEP states that it is not appropriate to take official notice of facts without citing a prior art reference where the facts asserted to be well known are not capable of instant and unquestionable demonstration as being well-known. *See also In re Ahlert*, 424 F.2d at 1091, 165 USPQ at 420-21.) The MPEP also states that the Examiner must provide documentary evidence in the next Office Action or withdraw the rejection. *See* 2144.03 C

Applicants submit that the Office's official notice is subject to reasonable dispute and does not meet the requirement of being well known or being capable of instant and unquestionable demonstration. Pickl found that their experiments failed when using serum-free media. (Pickl, p. 3851, under title "Cultivation of CD14+ cells"). Pickl had to use Fetal Calf Serum (FCS) in the media while incubating the CD14+ cells for the MLR assays to function. *Id.* The examples and studies disclosed in the present application

demonstrate to the contrary, that is, the present inventors found no such challenges when adding the third component, exogenous antigenic materials to trigger a specific immune response. Applicants overcame the problems of Pickl by co-incubating the two growth factors and the antigenic material, which is different from the method of Pickl. Therefore, Applicants respectfully request that the Examiner withdraw the rejection—or, provide documentary evidence that is recognized as standard in the pertinent art.

***REJECTIONS UNDER 35 U.S.C. § 102***

***Claims 44-46 are rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent No. 6,479,286 to Nelson et al.***

Claims 44-46 are rejected under 35 U.S.C. § 102 (e) as being anticipated by U.S. Patent No. 6,479,286 to Nelson et al. (hereinafter Nelson), which is said to disclose the claimed invention. The Office Action alleges that Nelson teaches a method for producing antigen loaded mature DCs comprising the steps of maturing monocytes in GM-CSF and TNF $\alpha$  (referring to claim 3); and it is said that the monocytes can be transfected with a gene encoding an antigen of interest, thus, satisfying the element of “the presence of a pre-processed antigenic material” (referring to column 15).

Applicants respectfully submit that the rejection fails to meet the standard of 35 U.S.C. § 102(b) because Nelson fails to teach each and every limitation of the claimed invention. In addition, Nelson does not anticipate the present application because Nelson’s elements are not arranged as required by the claims of the present application. The MPEP notes that in order to “anticipate a claim, the elements must be arranged as required by the claim.” MPEP 2131, Anticipation (citing *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990).

The Current Action alleges that Nelson’s claim 1 and 3 recite “incubating monocytes, as they mature into fully mature DC, in GM-CSF and TNF- $\alpha$ .” See the Current Action, at p. 5, para. 2, wherein Nelson claims a method wherein TNF- $\alpha$  is incubated with dendritic cells—not with monocytes as they mature. Nelson’s claim 1 discloses “incubating an expanded population [of monocytes] with GM-CSF and IL-4, thereby differentiating the expanding population of monocytes into dendritic cells.”

Claim 3 adds “incubating the dendritic cells with TNF- $\alpha$ , thereby activating the dendritic cells.” Thus, the step of incubating the cells with TNF- $\alpha$  can, necessarily, only follow the step of differentiating the monocytes into dendritic cells—but it cannot possibly occur before or simultaneously to treatment with GM-CSF and IL-4. Therefore, Nelson clearly teaches a multi-step protocol wherein first, monocytes are differentiated into dendritic cells (Nelson, claim 1); and second, TNF- $\alpha$  is added to differentiated dendritic cells (Nelson, claim 3). In contrast, the present application claims a single-step method wherein monocytes are matured with a tumor necrosis factor alpha and a granulocyte-macrophage colony-stimulating factor in the presence of an antigenic material to form mature antigen-presenting cells.

In addition, Nelson does not anticipate the present application because Nelson does not teach contacting with antigenic material. As referenced in the Current Action, Nelson teaches “Loading Dendritic cells by Transduction with a Gene Encoding a Peptide of Interest” (*see* Col. 15, pp. 20-21); in contrast, the present application claims “contacting with antigenic material.” The difference is substantial because it affects the processing of antigens, the presentation of antigens, and the mode as well as class of MHC involved. An overview of antigen presentation & MHC is provided by Khan Academy for convenience. *See* <http://www.khanacademy.org/video/professional-antigen-presenting-cells--apc--and-mhc-ii-complexes?playlist=Biology>.

Applicant respectfully submits that claims 44 to 46 are not anticipated by Nelson because Nelson does not identically disclose every element of the claimed invention. *See Corning Glass Works v. Sumitomo Electric*, 9 USPQ 2d 1962, 1965 (Fed. Cir. 1989). Applicants submit that a reference that excludes a claimed element, no matter how insubstantial or obvious, is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 USPQ 193, 198 (Fed. Cir. 1983). Nelson does not teach a single-step method and does not teach contacting with antigenic material. Therefore, Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 102(b). To more clearly set out the scope of the claimed subject matter, claim 44 was amended.

***Claims 44-47, 49, and 50 are rejected under 35 U.S.C. § 102 (b) as being anticipated by Proliferating Dendritic Cell Progenitors in Human Blood, Nikolaus Romani, et al.***

Claims 44-47, 49, and 50 are rejected under 35 U.S.C. § 102 (b) as being clearly anticipated by *Proliferating Dendritic Cell Progenitors in Human Blood*, Nikolaus Romani, et al., 1994 [hereinafter Romani], which is said to disclose the claimed invention.

The Current Action alleges that Romani teaches a method of producing antigen-loaded mature DCs comprising the step of maturing cord blood mononuclear cells in GM-CSF and TNF $\alpha$ . Concerning the missing element of “contacting with antigenic material,” the Current Action alleges that as the DCs matured, they would have inherently loaded themselves with antigen. In addition, the Current Action alleges the following: claim 49 is anticipated because cord blood comprises T cells; claim 50 is anticipated because any cell culture would inherently include some cell fractions and dying cells; that claim 47 is inherently anticipated because the cell culture medium comprises heat-treated FCS.

Applicants respectfully submit that the rejection fails to meet the standard of 35 U.S.C. § 102(b) as Romani fails to teach each and every limitation of the claimed invention. Romani does not anticipate the claims because the elements claimed to be inherently present are not necessarily present. The MPEP unmistakably states that for establishing inherency, the extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. MPEP 2112. Inherency, however, may not be established by probabilities or possibilities. The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993).

The Current Action does not provide any extrinsic evidence to support the allegation that the missing element is necessarily present, namely, an immunogenic

material. In fact, the Office admits that the alleged inherent characteristic is not present upon incubation in buffer alone; thus, the claimed inherent element is not necessarily present. For that reason, Romani is clearly not sufficient to support a rejection under 35 U.S.C. § 102 (b).

Applicants submit that the term antigen is commonly understood to be a molecule intended to or capable of being recognized by the immune system; i.e., a substance that is capable, under appropriate conditions, of inducing a specific immune response and of reacting with the products of that response. See <http://en.wikipedia.org/wiki/Antigen>; <http://www.answers.com/topic/antigen-2>; and <http://medical-dictionary.thefreedictionary.com/antigen>. Consequently, not every protein or fragment thereof constitutes an antigen. Romani does not teach the antigens of the present application; such antigens are not inherently present and the Office Action fails to provide extrinsic evidence that an induction of immune response specific for the “inherent antigen” has necessarily been selected, is necessarily intended, or necessarily accomplished. Therefore, Romani does not teach an antigen as disclosed in the present invention.

For the reasons outlined above, Applicants respectfully submit that claims 44-47, 49, and 50 are not anticipated by Romani. Romani does not identically disclose every element of the claimed invention, and such elements are not necessarily present. Therefore, Applicants respectfully request the Examiner withdraw the rejection under 35 U.S.C. § 102(b).

## CONCLUSION

In light of the remarks and arguments presented above, Applicants respectfully submit that the claims in the Application are in condition for allowance. Favorable consideration and allowance of the pending claims 44-50 are therefore respectfully requested.

Applicants believe this paper is being filed with all required fees. However, if any additional fee is due, including those for an extension of time please charge any fees required or credit any overpayment to Chalker Flores, LLP's Deposit Account No. 50-4863 during the pendency of this Application pursuant to 37 CFR 1.16 through 1.21 inclusive, and any other section in Title 37 of the Code of Federal Regulations that may regulate fees. If an extension of time is required with this response but is not included, Applicants hereby petition for a Request for Extension of Time under 37 CFR 1.136(a).

If the Examiner has any questions or comments, or if further clarification is required, it is requested that the Examiner contact the undersigned at the telephone number listed below.

Dated: November 24, 2010.

Respectfully submitted,  
CHALKER FLORES, LLP



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